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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/994,468	12/19/1997	STEWART D. LYMAN	2813-L	6662

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EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 04/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/994,468	LYMAN ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/16/04*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-26, 31-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-26 and 31-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment, filed 11/16/04, has been entered.
Claims 1-16 and 27-30 have been canceled.
Claims 19-20 have been amended.

Claims 17-26 and 31-36 are pending.

Claims 17-26 and 31-36 are pending and being acted upon presently.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Office Action will be in response to applicant's arguments, filed 11/16/04.
The rejections of record can be found in the previous Office Action (Paper Nos. 14/21/25).

3. As pointed out previously, applicant's amendment, filed 3/4/03, noted that the priority date of the instant claims enjoy the benefit of USSN 08/209,502, filed 3/7/94.

4. Upon applicant's request, filed 11/16/04, the previous requirement for formal drawings has been withdrawn.

5. Claims 17-26 and 31-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for hemopoietic cell expansion media comprising human or mouse flt3 ligand or comprising a soluble polypeptide consisting of amino acids 28-160 of SEQ ID NO: 6 does not provide enablement for hematopoietic cell expansion media comprising
"(a) polypeptides comprising amino acids 28-160 of SEQ ID NO: 6",
"(b) polypeptides comprising a fragment of amino acids 28-160 of SEQ ID NO: 6, wherein the fragment binds flt3",
"(c) a polypeptide that binds flt3 that is at least 90% identical to amino acids 28-160 of SEQ ID NO: 6 or
"(d) a fragment of (c) wherein the fragment binds flt3".

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's arguments, filed 11/16/04, have been fully considered but are not found convincing essentially for the reasons of record.
Applicant's arguments and the examiner's rebuttal are essentially the same as of record.

Applicant asserts that amending the claims to remove the term "flt3 ligand polypeptide" and to limit the claims to a specific human sequence SEQ ID NO: 6 does not permit the interpretation as reading on any "flt3 ligand polypeptide from any mammal".

Essentially, applicant asserts that the skilled artisan would not have to undertake undue experimentation to make and use the claimed invention because determining flt3 ligand polypeptides that are at least 90% identical to SEQ ID NO: 6 is considered routine in the art and therefore would not constitute undue experimentation.

Applicant relies upon the reduction to practice of two working examples of mouse and human flt3 ligand as well as direction and guidance as to how to make flt3 ligands variants that bind flt3 receptor in conjunction with known screening formats (e.g. pages 16-19 and Examples 10-11) would have resulted in routine experimentation at the time the invention was made.

Again, applicant is relying upon certain biological activities and the disclosure of a limited representative number of species to support an entire genus. The instant invention encompasses any "polypeptide comprising amino acids 28-160 of SEQ ID NO: 6" or "at least 90% identical to amino acids 28-160 of SEQ ID NO: 6"; yet the instant specification does not provide sufficient guidance and direction as to the structural features of said scope of the claimed "polypeptides / flt3 ligand polypeptides" and "fragments thereof" and the correlation between the chemical structure and the desired molecules or specificities. The reliance on the disclosed limited examples set forth in the specification does not support the enablement for any "polypeptide / flt3 ligand polypeptide" or "fragment thereof", encompassed by the claimed invention. For example, the disclosed mouse flt3 ligand polypeptides does not appear to be "at least 90% identical to amino acids 28-160 of SEQ ID NO: 6". In addition there is insufficient direction and guidance as to those amino acids that can be added to the core structure of amino acids 28-160 and still provide for a "polypeptide comprising amino acids 28-160 of SEQ ID NO: 6" that can expand hemopoietic cells.

Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality (e.g. ligand or receptor) requires a knowledge of and guidance with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which a polypeptide's structure relates to its functional usefulness. However, the problem of predicting polypeptide structure from mere sequence data of a single amino acid sequence and in turn utilizing predicted structural determinations to ascertain binding or functional aspects ligands and receptors and finally what changes can be tolerated with respect thereto is complex and well outside the realm of routine experimentation. In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

Because of the lack of sufficient guidance and predictability in determining which structures would lead to "flt3 ligand polypeptides" and "fragments"with the desired properties and that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) was not well understood and was not predictable (e.g. see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.); it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of "mammalian flt3 ligands" encompassed by the claimed invention.

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. Attwood (Science 2000; 290:471-473) teaches that "[i]t is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences. Similarly, Skolnick et al. (Trends in Biotech., 18(1):34-39, 2000) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2). In the absence of sufficient guidance and direction to the structural and functional analysis, applicant's reliance upon the mouse and human flt3 ligand disclosed in the specification as filed does not appear to provide sufficient enabling support for any mammalian flt3 ligand polypeptide and fragment thereof encompassed by the claimed invention and so the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Finally, even single amino acid differences can result in drastically altered functions between two proteins. For example, Metzler et al. (Nature Structural Biol. 1997; 4:527-531) show that any of a variety of single amino acid changes can alter or abolish the ability of CTLA4 to interact with its ligands CD80 and CD86 (e.g., summarized in Table 2).

A person of skill in the art is not enabled to make and use the "flt 3 polypeptide / flt3 ligand polypeptides" and "fragments thereof", as recited in the claims. A person of skill in the art would not know which sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences. There is insufficient guidance based on in vitro characterization assays to direct a person of skill in the art to select particular sequences as essential for the ability to bind flt3 for the expansion of hemopoietic cells. A person of skill in the art could not predict which particular amino acid sequences of "polypeptides / flt3 ligand polypeptides" and "fragments thereof" are essential and could be used in a hemopoietic cell expansion methods. It is not clear that the skilled artisan could predict the efficacy of the breadth to the "polypeptide / flt3 ligand polypeptides and "fragments thereof", encompassed by the claims, including "variants which may comprise conservatively substituted sequences" *page 8, lines 25-27 of the instant specification).

Without sufficient guidance, making and using "polypeptide / flt3 ligand polypeptide", including those that are "at least 90% identical to SEQ ID NO: 6" and "fragments thereof" would have been unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue

Applicant's arguments are not found persuasive.

7. Claims 17-26 and 29-36 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7, 9 and 10 of copending USSN 08/399,404 for the reasons of record..

Again, applicant's previous request for this rejection to be held in abeyance has been acknowledged.

8. No claim is allowed.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
April 19, 2004